Remarks

Claims 1-14, 17 and 67-68 are pending in the present application. Claims 1 and 17 are here amended to facilitate a finding of allowability. The Examiner in the Office Action finds new grounds for rejection, therefore a non-final Office Action is properly made.

Support for amendments to claims 1 and 17 are found in the claims as originally filed. No new matter is added by the amendments. Applicants reserve the right to pursue claims having the same or similar scope as the original claims in the present application, or in another application having the same filing and priority dates as the present application.

Applicants thank the Examiner for granting an interview, and for helpful comments at the interview of August 12, 2004.

Claim 17 as amended complies with U.S.C. § 112, second paragraph

The Office Action on p. 2, paragraph 4 of the Office Action rejects claim 17 under 35 U.S.C. § 112, second paragraph. Claim 17 is here amended to depend from claim 1, therefore this claim now complies with 35 U.S.C. § 112, second paragraph. Applicants respectfully request that this rejection be withdrawn.

Claims are nonobvious under U.S.C. § 103

The Office Action on p. 3, paragraph 7 rejects claims 1-8, 12-13, 17, and 67-68 under 35 U.S.C. § 103(a) in view of Cronin et al. (Human Mutation 7: 244-255, 1996) in combination with Solinas-Toldo et al. (Genes Chrom Cancer 20: 399-407, 1997), and further in view of Dorin et al. (Trends Biotech 9: 48-52, 1991) and Zielenski et al. (Nature Genetics 22: 128-129, 1999).

Applicants believe that a brief discussion of claim 1, from which all other claims herein depend directly or indirectly, would be helpful to the Examiner prior to discussing the cited art.

Claim 1 as here amended is directed to a method for generating a molecular profile of genomic DNA by hybridization of a genomic DNA to a plurality of immobilized nucleic acid probes. The probes are a collection of clones that represent a chromosome or a genome of an organism, and each clone is a member of a genomic library cloned in a vector and each probe is the vector having a cloned nucleic acid insert greater than about 50 kilobases. After contacting

the probes with a sample and observing an amount and location of labeled genomic nucleic acid hybridized to each probe to detect amplifications or deletions, positional information of hybridization of the clones on the arrays is correlated with observed amplifications or deletions, thereby generating a molecular profile of the chromosome or genome of the sample nucleic acid. The method of claim 1 is in wide use because it generates a molecular profile of the chromosome or the genome as is shown by the Appendix attached hereto (a partial list of publications showing such representations, as posted by Spectral Genomics, Inc., of Houston, TX, the licensee of the present claims).

None of the cited references alone or in any combination show, teach or suggest all of the features of claim 1, as shown below.

Cronin et al. (Human Mutation 7: 244-255, 1996)

Cronin refers to clinical tests for detecting cystic fibrosis (CF) mutations in DNA samples, by determining sequences in exon 11 of a gene on chromosome 7 associated with cystic fibrosis, CFTR. The Office Action on p. 5, paragraph C admits that the CF gene spans 250 kilobases (merely 0.25 megabases) of DNA. One of ordinary skill in the art of genomics, viewing chromosome 7 on the Human Genome Landmark Poster, would easily determine that Cronin's exon 11 is less than 0.2% of the 171 megabases of this chromosome.

Cronin in Fig. 1 (Id., p. 245) refers to four probes to interrogate each of four nucleotides, i.e., 16 probes are required to interrogate 0.000004 megabases. Further, Cronin's probes are 15-mers, i.e., have a length of 0.000015 megabases. Cronin's first set of 428 tiled 15-mer probes interrogates less than 30 such four nucleotide sequences, so resolves about 120 bases of sequence (0.000120 megabases). Cronin's second set of 1480 probes interrogates 37 mutation-specific sequences (Id., p. 246, right column, first paragraph), each of which may be about 10 nucleotides in length (0.000010 megabases; Id, p. 250, Fig. 3A). In fact, the Office Action admits on p. 5, lines 8-10 that Cronin does not teach probes generating a molecular profile of a chromosome or a genome, and does not teach probes which are a vector having nucleic acid inserts greater than about 50 kilobases. Because Cronin uses very short probes, this reference teaches away from probes that are a vector, and having inserts greater than 50 kilobases.

Applicant's claims are directed to products that detect syndromes affecting large portions of one or more chromosomes, and claim 1 features a plurality of probes that are the vector having

clones that represent a chromosome or a genome. Cronin represents only an infinitesimally small portion of a chromosome.

For any of these reasons, Cronin fails to teach or suggest the invention of claim 1 as here amended. Applicants assert that none of the other references cited by the Examiner, alone or in combination, cure these deficiencies of Cronin et al.

Solinas-Toldo et al. (Genes Chrom Cancer 20: 399-407, 1997)

Solinas-Toldo et al. refers to use of chips to detect high copy number amplication and low copy number gains and losses for cancer genes (Solinas-Toldo et al., Abstr. lines7-9). Nine different tumors were used as sources of samples (Id., p. 401, Table 1 line 4). Solinas-Toldo's data show that the colon carcinoma cell line Colo320 HSR and the promyelocytic leukemia cell line HL60 each contains a high-copy-number amplification of oncogene *MYC* (Id., p. 403, left col.). Visual inspection of the chip distinguishes the high-copy-number amplifications (Fig. 1; Id., p. 403).

Further, a map of two regions of locus 13q14 is shown in Fig. 3 (Id., p. 405). A reference bar for length of DNA is provided in Fig. 3, and by extrapolation from this bar to the entire length shown in Fig. 3, one of ordinary skill in genetics can determine that the length of each region is about 500 kb (0.5 megabases). Chromosome 13, for comparison, is about 113 megabases in length, i.e., Fig. 3 of Solinas-Toldo et al. shows less than 1% of that chromosome, less than two orders of magnitude of what is provided by the method of claim 1 as here amended.

Solinas-Toldo et al. fails to remedy the defects in Cronin et al., because Solinas-Toldo et al. fails to teach or show probes that represent the chromosome, let alone the genome.

Dorin et al. (Trends Biotech 9: 48-52, 1991)

Dorin et al. is a review of the status of CF genetics, cloning, and screening technologies for correlating phenotype with genotype. Fig. 1 (Dorin et al., p. 405) shows a co-linear map of the CFTR exons and functional positions in the CFTR protein. Like Cronin et al. and Solinas-Toldo et al., Dorin et al. does not teach or suggest a representation of a chromosome, let alone a genome.

Dorin fails to remedy the defects in Cronin et al., because this reference fails to teach or show probes that represent all of the chromosome, or all of the genome.

Zielenski et al. (Nature Genetics 22: 128-129, 1999)

Zielinski et al. refers to to the disease "meconium ileus" (MI), which is a severe intestinal obstruction, and analyzes data correlating symptoms of MI with presence in patients of a CF modifier locus on human chromosome 19q13 (Zielinski et al., p. 128, left col., first paragraph). The method analyzes for presence of any of nine polymorphic microsatellite markers spanning a 7.65-Mb region from 19q13.2 to q13.4 in a large sample of CF sib pairs and parents (Id., p. 128, left col., last paragraph). By contrast, chromosome 19 has a total length of about 61 megabases. Fig. 1 of Zielinski refers to a statistical analysis of MI phenotype for markers in the q13 region, and is not a representation of a chromosome or a genome.

Zielinski et al. fails to remedy the defects in Cronin et al., because this reference fails to teach or show probes that represent the chromosome, let alone the genome.

Neither of Solinos-Toldo, Dorin or Zielinski et al. remedy the defects of claim 1, therefore claim 1 is not obvious in view of these references. Claims 2-8, 12-13, 17, and 67-68 depend directly or indirectly from claim 1, and incorporate all of the features of claim 1. As none of the references cited in combination with Cronin et al. cure the deficiencies in Cronin et al., Applicants request that rejection of claims 1-8, 12-13, 17, and 67-68 under 35 U.S.C. § 103 (a) in view of this combination of references be withdrawn.

Waggoner et al. (U.S. patent number 5,268,486)

The Office Action on p. 7, paragraph 8 rejects claim 9 in view of Cronin et al, Solinas-Toldo et al., Dorin et al., Zielenski et al., and Waggoner et al. (U.S. patent number 5,268,486). As claim 9 depends indirectly from claim 1 and includes all of the features of claim 1, Waggoner will be characterized insofar as it can be combined with Solinas-Toldo, Dorin, and Zielenski to remedy the defects of Cronin et al. with respect to features of claim 1.

Waggoner describes fluorescent arylsulfonate dyes, including their chemical properties with respect to reacting them with molecules of interest, and physical properties with respect to excitation and fluorescence.

Waggoner simply does not teach or suggest probes that are the vector having inserts of greater than 50 kB and that represent the chromosome or even the genome, as is required by claim 1 as here amended. Waggoner et al. fails to remedy the deficiencies of Cronin et al., which

as discussed above are not remedied by any of Solinas-Toldo, Dorin, and Zielenski alone or in any combination.

As claim 9 depends indirectly from claim 1 and incorporates all of the features of claim 1, Waggoner does not render claim 9 obvious, alone or in combination with any or all of the other references cited in the Office Action.

Anderson et al. Nucl. Acids Res. 9:3015-3027 (1981)

The Office Action on p. 7, paragraph 9 rejects claim 10 under 35 U.S.C. § 103(a) over Cronin in view of Solinas-Toldo et al., Dorin et al., Zielenski et al., and further in view of Anderson et al. Nucl. Acids Res. 9:3015-3027 (1981). As claim 10 depends indirectly from claim 1, and includes all of the features of claim 1, Anderson will be characterized insofar as it can be combined with Solinas-Toldo, Dorin, and Zielenski with respect to features of claim 1.

Anderson refers to a method of sequencing, and for sequencing a 4257 bp (0.004 megabases) fragment of bovine mitochondrial DNA. See Anderson et al., Abstract. The method involves preparing a library of random cloned subfragments and sequencing each subfragment, then reconstructing the entire length, i.e., 0.004 megabases, from the individual sequences.

Anderson et al. fails to cure the deficiencies of Cronin et al. and the other references cited by the Office Action, because Anderson et al. fails to teach or suggest probes that are a vector having inserts of greater than about 50 kB, that represent the chromosome or the genome, as is the subject matter of claim 1 as here amended. Anderson shows only a fragment of bovine mitochondrial DNA, which is infinitesimally small compared to the length of a chromosome, let alone a genome. As claim 10 depends indirectly from claim 1, and includes all of the features of claim 1, this claim is not obvious in view of Anderson alone or in combination with Cronin or any of the other references cited by the Office Action.

Ordahl et al., Nucl. Acids Res. 3:2985-99 (1976)

The Office Action on p. 8, paragraph 10 rejects claim 11 under 35 U.S.C. § 103(a) in view of Cronin, in combination with Solinas-Toldo et al Dorin et al., Zielenski et al., in combination with Anderson and Ordahl et al., Nucl. Acids Res. 3:2985-99 (1976). As claim 11 depends indirectly from claim 1, and includes all of the features of claim 1, Ordahl will be

characterized insofar as it can be combined with Solinas-Toldo, Dorin, Zielenski and Anderson, with respect to curing the deficiencies of features of claim 1.

Ordahl et al. is a comparison of five sizing techniques for DNA fragments produced by shearing in a French press. This reference concludes that the sizes are overestimated by the Kleinschmidt electron microscopy visualization and by velocity sedimentation techniques (see Ordahl, Abstract).

Like the other references cited by the Office Action, Ordahl et al. fails to cure the deficiencies of Cronin et al. because Ordahl et al. fails to teach or suggest any probes, let alone probes that represent all of a chromosome, or all of a genome, as is the subject matter of claim 1 as here amended. Ordahl shows only fragments on the order of hundreds of base pairs, which is a size that is infinitesimally small compared to the length of all of a chromosome or a genome. As claim 11 depends indirectly from claim 1, it incorporates all of the features of claim 1, therefore it is not obvious in view of Ordahl alone or in combination with Cronin et al., or with any of the other references cited by the Office Action.

Analysis according to relevant case law

For additional reasons shown below, the subject matter of the claims would not have been obvious in light of the prior art of record, i.e., the subject matter of claim 1 as here amended is neither taught nor suggested by the references of record, Cronin et al., Solinas-Toldo et al., Dorin et al. and Zielinski et al., alone or in combination with eachother, or in combination with one or more of Waggoner, Anderson, or Ordahl.

The courts in *In re Vaeck,* 20 U.S.P.Q. 2d 1438, 947 F.2d 488 (Fed. Cir. 1991), *In re Bell,* 26 U.S.P.Q. 2d 1529, 991 F. 2d. 781 (Fed. Cir. 1993), and in *Hybritech v. Monoclonal Antibodies,* 231 U.S.P.Q. 81, 802 F. 2d 1367 (F. Cir. 1986) state that a first question in deciding whether a prima facie case of obviousness can be made is whether the references suggest the invention.

To establish a *prima facie* case of obviousness, it must be shown: first, that there is some suggestion or motivation, either in the reference or in the knowledge cited available to one of ordinary skill in the art, at the time the invention was made, to modify the reference to obtain the invention and second, that the prior art reference teaches or suggests all the limitations of the claim. (Manual of Patent Examining Procedure 2143). We show above that Cronin et al. and the

other references fail to satisfy these criteria, alone or in any combination, therefore a *prima facie* case of obviousness has not been made. Thus, rejection of claims 1-8, 12-13,17 and 67-68 in light of Cronin et al. further in view of Solinas-Toldo et al., Dorin et al. and Zielinski et al.on the basis of 35 U.S.C. §103(a) is improper because none of these references cure the deficiencies of Cronin et al. These references have been characterized above, and case law as applied to the various combinations is now considered. .

No aspects of Cronin et al. teach or suggest a collection of probes that are a vector having inserts of greater than 50 kB, i.e., clones that represent all of a chromosome or a genome of an organism. While Solinas-Toldo et al. briefly refers to whole chromosomes in a discussion of principles (p. 400, left col., last paragraph) in the background section, and to the human genome (p. 406, left col., last paragraph), these are mere theoretical speculations. The discussion in Solinas-Toldo is followed by the remark, "...might become a feasible approach." This final remark is hardly the prediction of success that would be incentive to combine this reference with Cronin et al., even if Solinas-Toldo were to suggest the combination which it does not. Further, other different types of chips are suggested in Solinas-Toldo. A mere mention is not sufficient to render claim 1 as here amended obvious, in combination with Cronin et al. or any of the other cited references.

Even if Solinas-Toldo et al. or any of the other references were considered to provide an incentive to use a library of probes to represent all of a chromosome or a genome, such a general incentive is not sufficient to render the present invention obvious in view of Cronin et al.

When there are no specific teachings in the cited art, such art cannot form the basis of a rejection for obviousness. "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *See In re Deuel*, 34 U.S.P.Q. 2d 1210, 1216, 51 F. 3d 1552 (Fed. Cir. 1995) following *In re O'Farrell*, 7 U.S.P.Q. 2d 1673, 1680-1681, 853 F. 2d 1673 (Fed. Cir. 1988).

"Obviousness 'cannot be established by combining teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination.' " *In re Bell,* 26 U.S.P.Q. 2d 1529, 1531, 991 F.2d 781 (Fed. Cir. 1993, citing *In re Fine*, 5 U.S.P.Q. 2d 1529, 837 F. 2d 1071 (Fed. Cir. 1988), which in turn was citing *A.C.S. Hospital System v. Montefiore Hospital*, 221 U.S.P.Q. 215, 732 F. 2d 1571, (Fed. Cir. 1984)). [Emphasis added.]

None of these references direct the artisan of ordinary skill to the other references that in combination are asserted to render obvious the invention of the present claims. In particular, Cronin, Solinas-Toldo and Zielinski, published in 1996, 1997 and 1999, respectively, fail to cite even one of Dorin, Waggoner, Anderson or Ordahl, which were published in 1991, 1983 and 1976, respectively. Over 20 years elapsed from publication of Ordahl to publication of Cronin, yet Ordahl is not suggested as a combination by any of Cronin or the even later published Solinas-Toldo and Zielinski.

This factual analysis indicates that none of the references cited provides teachings or suggestions that direct one of ordinary skill in art, at the time the present invention was made, to the other references cited. By standards of the established case law, Applicants' invention would not have been obvious in view of the combination of references.

Moreover, that a method may be "obvious to try", is not a basis for rejection under 35 U.S.C. § 103. See *In re O'Farrell*, 7 U.S.P.Q. 2d 1673, 1680-1681, 853 F. 2d 1673 (Fed. Cir. 1988). A reference must not only suggest additions or modifications, but the reference must also suggest that such changes would be successful. *In re O'Farrell*, 7 U.S.P.Q. 2d 1673, 1680-1681, 853 F. 2d 1673 (Fed. Cir. 1988).

None of Solinas-Toldo, Dorin et al., and Zielinski et al. addresses any of the deficiencies noted above in Cronin et al., therefore these references fail to suggest any changes as to what is directly shown in this reference. Further, the different methods used and the different conclusions reached by the references mean that no success could have been obvious for any experiment based on the combination of these references. See *In re Dow Chemical Co.,* 5 U.S.P.Q. 2d 1529, 837 F.2d 469 (Fed. Cir. 1988).

Courts have found that unexpected properties of an invention can render the invention unobvious over prior art. In *Ex parte Gray*, 10 U.S.P.Q. 2d 1922 (Bd. Pat. App. & Interf. 1988), an obviousness rejection of recombinantly produced human nerve growth factor in light of references disclosing this protein from placental tissue was not supported. In this case the Board stated that the dispositive issue is whether the "claimed factor exhibits any unexpected properties compared with that described by cited publication items." [Emphasis added.] Further, an unexpected property can be possessed by the unobvious novel material merely "to an unexpectedly greater degree". *In re Dillon*, 16 U.S.P.Q. 2d 1897, 918 F. 2d 688 (Fed. Cir. 1990). In fact, to be patentable a compound need not have excelled over prior art compounds in all

common properties; it is sufficient if the evidence shows that the compound was unexpectedly superior in merely one of a spectrum of common properties. *In re Chupp*, 2 U.S.P.Q. 2d 1437, 1439, 816 F. 2d 643, 646 (Fed. Cir. 1987), and *Ex parte A*, 17 U.S.P.Q. 2d 1716, 1719 (Bd. Pat. App. & Interf. 1990).

No collection of probes that are a vector having inserts of greater than 50 kB, i.e., a collection of clones that represent a chromosome or a genome of an organism, was taught or suggested by Cronin et al., wherein positional information of clones on the arrays and chromosomes is correlated. In fact, Cronin et al. use as probes simple short synthetic nucleotides. Applicants' licensee's products are routinely used to make such representations of entire genomes. See the Appendix attached hereto. In particular, see Gunn et al., Am. J. Medical Genetics p. 1-9, 2003, showing in Fig. 5 a representation of all of chromosomes 18 and 4 to diagnose a translocation between these chromosomes. Spectacular diagnosis of the syndrome by Gunn et al. using the method of claim 1 is not obvious in view of Cronin in combination with any of the references cited in the Office Action. See also other references listed in the Appendix for further representations of chromosomes or genomes, using the method of claim 1.

As stated in *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991), "...both suggestion and reasonable suggestion of success must be found in the prior art, not in Applicant's disclosure." It is improper for the Examiner to reconstruct the invention by using the application as a blueprint by which to join unrelated prior art.

In this case, none of these prior art references even mentions, let alone suggests, the element of all of the present claims, viz., a method of generating a molecular profile of genomic DNA by hybridization to a plurality of immobilized probes, the plurality being a collection of clones that represent all of a chromosome or a genome, each probe is a member of a genomic library cloned in a vector, and each probes is the vector having a cloned nucleic acid insert greater than about 50 kilobases, and the plurality of probes represent all of the chromosome or genome. None of the references suggests positional information of clones on arrays and chromosomes being correlated, to generate a molecular profile of the chromosome or genome of the sample nucleic acid.

Instead, the prior art references here do not provide any probes that represent even significant portions, let alone all of any chromosome at all, let alone an entire genome (Waggoner, Ordahl, Anderson). At best, the references cited by the Examiner represent merely a

function such as a correlation of symptoms with a portion of a gene, not a chromosome (Zielinski et al.), or represent a domain of a protein with a map of exons of a gene that is a mere fraction of a chromosome (Dorin et al.), or represent hybridization of sample nucleic acid to a portion of a gene that is a minute fraction of a chromosome (Cronin et al. and Solino-Toldo et al.).

None of the references teach or suggest the present claims, nor suggest a combination, nor suggest success were such a combination even suggested. Therefore the invention cannot be obvious in light of any combination of the references cited by the Examiners.

Applicants respectfully request that the Examiners withdraw rejection of the claims under 35 U.S.C. §103.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance.

If the Examiner has any questions regarding these amendments and remarks, the Examiner is encouraged and invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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